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HEALTH EFFECTS ASSESSMENT
FOR 2,4,6-TRICHLOROPHENOL

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
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U.S. Environmental Protection Agency
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16. ABSTRACT This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes. A q_1^* was determined for 2,4,6-trichlorophenol based on oral exposure.		
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with 2,4,6-trichlorophenol. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) source has been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Chlorinated Phenols. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-032. NTIS PB 81-117-434.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment in proper context, the reader is referred to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates.

2,4,6-Trichlorophenol has been shown to be carcinogenic in both rats and mice following oral administration. Data are not available which address the carcinogenicity of this compound in human populations. Limited mutagenicity testing has yielded mixed results. Using data for hepatocellular carcinoma and adenoma incidence in male mice, a q_1^* of 1.98×10^{-2} (mg/kg/day)⁻¹ was calculated. No data are available which address the potential carcinogenicity of this compound by the inhalation route.

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TABLE OF CONTENTS

	<u>Page</u>
1. ENVIRONMENTAL CHEMISTRY AND FATE.	1
2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS	3
2.1. ORAL	3
2.2. INHALATION	3
3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS	4
3.1. SUBCHRONIC	4
3.1.1. Oral.	4
3.1.2. Inhalation.	6
3.2. CHRONIC.	6
3.2.1. Oral.	6
3.2.2. Inhalation.	7
3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS.	8
3.4. TOXICANT INTERACTIONS.	8
4. CARCINOGENICITY	9
4.1. HUMAN DATA	9
4.2. BIOASSAYS.	9
4.3. OTHER RELEVANT DATA.	13
4.4. WEIGHT OF EVIDENCE	13
5. REGULATORY STANDARDS AND CRITERIA	14
6. RISK ASSESSMENT	15
6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)	15
6.2. ACCEPTABLE INTAKE CHRONIC (AIC).	15
6.3. CARCINOGENIC POTENCY (q_1^*)	15
6.3.1. Oral.	15
6.3.2. Inhalation.	15
7. REFERENCES.	16
APPENDIX: Summary Table for 2,4,6-Trichlorophenol.	19

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
MED	Minimum effective dose
ppm	Parts per million
RV _d	Dose-rating value
RV _e	Effect-rating value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Relevant physical and chemical properties and environmental fate of 2,4,6-trichlorophenol (CAS No. 88-06-2) are as follows:

Chemical class:	halogenated phenol	
Molecular weight:	197.46	Verschueren, 1983
Vapor pressure: (estimated)	0.012 mm Hg at 25°C	Mabey et al., 1981
Water solubility:	800 mg/l at 25°C	Verschueren, 1983
Log octanol/water partition coefficient:	3.87	U.S. EPA, 1980b
Bioconcentration factor:	310 in Golden orfe (<u>Leucisens idus</u> <u>melanotus</u>)	Freitag et al., 1982
Half-life in Air:	<1 day (estimated)	
Water:	<1-19 days (estimated)	
Soil:	5 days for complete biodegradation	Verschueren, 1983

The half-life for 2,4,6-trichlorophenol in the atmosphere is estimated from its relative photodecomposition rate (silica gel coated material) with respect to the photodecomposition of pentachlorophenol as determined by Freitag et al. (1982) and the half-life for photodecomposition of pentachlorophenol in aquatic media as estimated by Callahan et al. (1979). The lower value for the half-life range in aquatic media as given above is based on considerations similar to those of atmospheric photodecomposition. In aquatic media, however, photodecomposition may become less significant as the water depth increases because of light scattering and resulting attenuation. Therefore, precipitation through adsorption onto particulate matter

(Freitag et al., 1982) and biodegradation may play significant roles in determining the fate of this chemical in certain bodies of water. The upper value for the half-life range has been speculated from the estimated biotransformation rate constant (3×10^{-9} $\text{mg cell}^{-1} \text{ hr}^{-1}$) reported by Mabey et al. (1981) and the concentration of microorganisms at 5×10^5 cells mg^{-1} (Burns et al., 1982).

The octanol/water partition coefficient value indicates that this compound may be sorbed significantly to soils with high organic carbon content. In sandy soils, 2,4,6-trichlorophenol may have significant mobility. The biodegradability of this compound in soils may prevent substantial contamination of groundwater because of leaching.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL MAMMALS

2.1. ORAL

No quantitative studies of gastrointestinal absorption of 2,4,6-trichlorophenol have been found in the available literature; however, Dougherty and Piotrowska (1976) suggested that chlorophenols as a chemical class tend to be excreted rapidly through the urine and, therefore, urinary concentrations should reflect exposure. Quantitative analyses were not performed in this study.

2.2. INHALATION

Pertinent data regarding the absorption of 2,4,6-trichlorophenol following inhalation exposure could not be found in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. No reports of toxicity in humans associated with subchronic oral exposure to 2,4,6-trichlorophenol could be found in the available literature. The only investigation of the subchronic oral toxicity to animals of 2,4,6-trichlorophenol was a range-finding experiment by the NCI (1979) preliminary to performing an oral carcinogenicity bioassay. In this study, groups of five male and five female Fischer 344 rats were fed ad libitum diets that contained 0, 10,000, 14,700, 21,500, 31,500 or 46,000 ppm 2,4,6-trichlorophenol for 7 weeks followed by 1 additional week of observation. Mortality, body weights and histopathological evaluation of selected organs were the parameters of toxicity that were monitored. Groups of five B6C3F₁ mice of each sex were also fed ad libitum diets containing 0, 6800, 10,000, 14,700, 21,500 or 31,500 ppm 2,4,6-trichlorophenol for 7 weeks followed by an additional 1-week observation period. The same parameters of toxicity were monitored in mice as in rats.

Body weight and survival data for both rats and mice are presented in Table 3-1. Mean body weights for treated rats and mice of each sex were considerably lower than those of corresponding controls. This trend appeared to be strongly dose-related, although statistical analyses were not performed. In rats, histopathological lesions were found only in the high-dose groups and consisted of moderate to marked increases in splenic hemopoiesis in rats of each sex and midzonal vacuolization of hepatocytes in two male rats. All tissues from mice exposed to diets containing 21,500 ppm 2,4,6-trichlorophenol appeared to be essentially normal. The evaluation of toxicity was insufficient to enable this study to be used in quantitative risk assessment.

TABLE 3-1

2,4,6-Trichlorophenol Subchronic Feeding Studies in Rats and Mice^a

Dose (ppm)	Male		Female	
	Survival ^b	Mean Weight at Week 7 as % of Control	Survival ^b	Mean Weight at Week 7 as % of Control
<u>Rats</u>				
0	5/5	100	5/5	100
10,000	5/5	96	5/5	92
14,700	5/5	89	5/5	84
21,500	4/5	73	5/5	73
31,500	4/5	47	4/5	67
46,000	3/5	39	2/5	42
<u>Mice</u>				
0	5/5	100	4/5	100
6,800	5/5	99	5/5	110
10,000	5/5	99	5/5	110
14,700	5/5	83	5/5	101
21,500	5/5	79	5/5	93
31,500	3/5	57	3/5	68

^aSource: NCI, 1979^bNumber surviving/number in group

3.1.2. Inhalation. Pertinent data regarding toxicity in humans or animals related to inhalation exposure to 2,4,6-trichlorophenol could not be located in the available literature.

3.2. CHRONIC

3.2.1. Oral. No reports of toxicity in humans chronically exposed to 2,4,6-trichlorophenol by the oral route could be found in the available literature. Likewise, no investigations of chronic oral toxicity of 2,4,6-trichlorophenol in laboratory animals suitable for quantitative risk assessment could be found in the available literature.

BRL (1968) administered commercial grade 2,4,6-trichlorophenol (impurities unspecified) to groups of 18 male and 18 female C57B1/6 x C3H/Anf F₁ mice and 18 male and 18 female C57B1/6 x AKR F₁ mice. From 7-28 days of age, mice were treated by gavage with 100 mg 2,4,6-trichlorophenol in 0.5% gelatin/kg bw. The amount administered remained unchanged; adjustments for changes in body weight were not made. At 28 days of age, gavage treatment was discontinued and all four groups of mice were exposed to diets containing 260 ppm 2,4,6-trichlorophenol. Treatment was continued to 78 weeks of age. Survival was the only parameter of toxicity evaluated. At the end of the experiment, survival in the above four groups was 10/18, 16/18, 16/18 and 17/18, respectively. Tumor data are reported in Section 4.2.

The NCI (1979) completed a carcinogenicity bioassay in which groups of 50 male and 50 female Fischer F344 rats were exposed to 5000 or 10,000 ppm 2,4,6-trichlorophenol in the diet for 106-107 weeks. Matched controls consisted of 20 untreated rats of each sex. Groups of 50 male B6C3F₁ mice were fed diets containing 5000 or 10,000 ppm 2,4,6-trichlorophenol for 105 weeks. Groups of 50 female B6C3F₁ mice were fed diets containing 10,000 or 20,000 ppm 2,4,6-trichlorophenol for 38 weeks. Because of severe body

weight loss in the treated female mice, dosages were reduced to 2500 and 5000 ppm, respectively, and treatment was continued for an additional 67 weeks. Matched controls consisted of 20 untreated mice of each sex. Body weights were recorded monthly; all animals were subjected to necropsy at death (unless cannibalized), when moribund or at the termination of the experiment.

Treated rats of each sex exhibited mean body weights lower than those of matched controls. Statistical analyses of body weight data were not reported; however, estimates of the probability of survival for treated male and female rats and for matched controls were subjected to statistical analysis. No significantly dose-related trend in mortality in rats of either sex was found by the Tarone test. Other clinical signs of toxicity (not specified) were common to both treated and control groups.

Mean body weights of treated mice of each sex were lower than those of corresponding controls and were dose-related throughout the experiment. By the Tarone test, no significant dose-related trend in mortality was found in mice of either sex. Other clinical signs of toxicity (not specified) were common to both treated and control groups.

The incidence of neoplasms associated with 2,4,6-trichlorophenol in this bioassay is discussed in Section 4.2.

3.2.2. Inhalation. No reports of toxicity in humans or animals associated with chronic inhalation exposure to 2,4,6-trichlorophenol could be found in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

No reports could be found in the available literature associating teratogenicity, fetotoxicity or reproductive toxicity with oral or inhalation exposure to 2,4,6-trichlorophenol.

3.4. TOXICANT INTERACTIONS

No studies of the interactions of 2,4,6-trichlorophenol with other xenobiotics could be found in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

No reports of cancer in humans associated specifically with 2,4,6-trichlorophenol have been found in the available literature.

4.2. BIOASSAYS

An oral bioassay in (C57B1/6 x C3H Anf) F₁ mice and (C57B1/6 x AKR) F₁ mice has been performed by BRL (1968). The experimental protocol and survival data to 78 weeks of age are discussed in Section 3.2.1. Among C57B1/6 x C3H Anf F₁ mice the tumor incidence was 9/18 for males and 7/18 for females (types of tumors not specified). Among C57B1/6 x AKR F₁ mice, tumors were found in 3/17 males and 2/17 females. In pooled controls, tumors were found in 22/79, 8/87, 16/90 and 7/82 in C57B1/6 x C3H Anf F₁ males and females and in C57B1/6 x AKR F₁ males and females, respectively. Statistically significant increases ($p < 0.05$) in the incidences of hepatomas (5/36) and reticulum cell sarcomas (6/36) were observed in C57B1/6 x C3H Anf F₁ mice when the numbers of tumors in males and females were combined and compared with pooled controls. IARC (1979) noted that the statistical significance disappears when the incidence of tumors in males and females are considered separately or when incidences of tumors in treated mice are compared with the incidences in matched controls.

The NCI (1979) has completed an oral bioassay in Fischer F344 rats and B6C3F₁ mice. The details of the protocol were discussed in Section 3.2.1. Fifty rats of each sex and groups of 50 male mice were fed ad libitum with diets containing 5000 or 10,000 ppm 2,4,6-trichlorophenol for 105-107 weeks. In addition, 50 female mice were exposed initially to diets containing 10,000 or 20,000 ppm 2,4,6-trichlorophenol for 38 weeks, and

subsequently to diets containing 2500 or 5000 ppm for an additional 67 weeks. TWA exposures in female mice were 5214 and 10,428 ppm 2,4,6-trichlorophenol, respectively.

In rats, the incidence of neoplasms of the hematopoietic system, lymphoma and monocytic leukemia appeared to be treatment-related. These data are detailed in Table 4-1. The elevated incidence of monocytic leukemia in male rats was statistically significant, with p values for the Fisher exact test of 0.013 and 0.002 associated with the low- and high-dose groups, respectively. The Cochran-Armitage test for a positive dose-related trend was also significant ($p=0.003$). The incidence of monocytic leukemia in female rats was not statistically significant by either test. The NCI (1979) stated that the "statistical conclusion is that the incidence of [monocytic leukemia] in male rats is associated with the administration of 2,4,6-trichlorophenol."

In mice, the incidence of hepatocellular neoplasms appeared to be high in all treated groups but especially high in the two groups of treated male mice, where most of the livers were affected. These data are summarized in Table 4-2. In male mice the elevated incidence of hepatocellular neoplasms (carcinomas or adenomas) in either treated group was significant ($p<0.001$) by the Fisher exact test when compared with controls. The result of the Cochran-Armitage test for a positive dose-related trend for hepatocellular neoplasia in male mice was also highly significant ($p<0.001$). The elevated incidence of hepatocellular carcinoma in treated female mice was significant by the Cochran-Armitage test ($p=0.005$) but not by the Fisher exact test. When the incidence of hepatocellular carcinoma or adenoma in treated female mice was compared with the incidence of these tumors in control mice the

TABLE 4-1

Incidence of Neoplasia of the Hematopoietic System
in Male and Female Rats Exposed to 2,4,6-Trichlorophenol*

	Males			Females		
	Control	Low-Dose	High-Dose	Control	Low-Dose	High-Dose
Number of animals necropsied	20	50	50	20	50	50
Malignant lymphoma	1 (5%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (4%)
Monocytic leukemia	3 (15%)	23 (46%)	29 (58%)	3 (15%)	11 (22%)	11 (22%)
Fisher exact	NR	(p=0.013)	(p=0.002)	NR	NS	NS
Cochran-Armitage test	(p=0.003)	NR	NR	NS	NR	NR

*Source: NCI, 1979

NS = Not statistically significant; NR = Not reported

TABLE 4-2
Incidence of Hepatic Neoplasia in Male and Female Mice Exposed to 2,4,6-Trichlorophenol*

	Males			Females		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
Number of animals with tissues examined microscopically	20	49	47	20	50	48
Hepatocellular adenoma	3 (15%)	22 (45%)	32 (68%)	1 (5%)	12 (24%)	17 (35%)
Hepatocellular carcinoma	1 (5%)	10 (20%)	7 (15%)	0 (0%)	0 (0%)	7 (15%)
Fisher exact test	NR	NS	NS	NR	NS	NS
Cochran-Armitage test	NS	NR	NR	(p=0.005)	NR	NR
Total hepatocellular tumors	4 (20%)	32 (65%)	39 (83%)	1 (5%)	12 (24%)	24 (50%)
Fisher exact test	NR	(p<0.001)	(p<0.001)	NR	NS	(p<0.001)
Cochran-Armitage test	(p<0.001)	NR	NR	(p<0.001)	NR	NR

*Source: NCI, 1979

NS = Not statistically significant; NR = Not reported

Fisher exact test was significant for the high-dose group ($p < 0.001$) and the Cochran-Armitage test indicated ($p < 0.01$) a positive dose-related trend. Data regarding the incidence of hepatocellular carcinomas and adenoma in male mice were selected by the U.S. EPA (1980b) for derivation of a q_1^* (Section 6.3.1.).

4.3. OTHER RELEVANT DATA

Negative results for mutagenicity in the Ames Salmonella typhimurium bioassay were obtained for 2,4,6-trichlorophenol both with and without the addition of rat hepatic S9 activation (Rasanen et al., 1977). In S. cerevisiae strain MP-1, 2,4,6-trichlorophenol increased the mutation rate but not the rate of intragenic recombination (Fahrig et al., 1978).

4.4. WEIGHT OF EVIDENCE

No reports of cancer in humans linked to 2,4,6-trichlorophenol have been found in the available literature. The significant ($p < 0.05$) incidence of "total tumors" in C57B1/6 x C3H Anf F_1 mice compared with pooled controls in the study by BRL (1968) suggested that 2,4,6-trichlorophenol may be carcinogenic. The NCI (1979) bioassay discussed in Section 4.2. indicated that monocytic leukemia in male rats was associated with dietary intake of 2,4,6-trichlorophenol. In both male and female mice, the incidence of hepatocellular neoplasia (adenoma and carcinoma) was significantly ($p < 0.001$) linked to dietary exposure to 2,4,6-trichlorophenol. Judging the degree of evidence for carcinogenicity in humans to be inadequate and the degree of evidence for carcinogenicity in animals to be adequate, 2,4,6-trichlorophenol is most appropriately classified according to the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984) in Group B2 - Probable Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

No current standards or recommended criteria for 2,4,6-trichlorophenol in air were found in the available literature. The U.S. EPA (1980b) has not recommended an ambient water quality criterion for 2,4,6-trichlorophenol based on chronic toxicity because of the carcinogenic nature of this compound. An acceptable concentration of 12 $\mu\text{g}/\text{l}$ based on an increased carcinogenic potency was recommended. A criterion to protect against organoleptic effects of 2.0 $\mu\text{g}/\text{l}$ was also proposed, based on the data of Deitz and Traud (1978).

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

2,4,6-Trichlorophenol is a chemical known to be carcinogenic in animals and for which data are adequate for derivation of a q_1^* . It is inappropriate, therefore, to calculate an AIS for 2,4,6-trichlorophenol.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

2,4,6-Trichlorophenol is a chemical known to be carcinogenic in animals and for which data are adequate for derivation of a q_1^* . It is inappropriate, therefore, to calculate an AIC for 2,4,6-trichlorophenol.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. Dietary treatment of male mice with TWA concentrations of 5000 and 10,000 ppm 2,4,6-trichlorophenol resulted in a highly significant ($p < 0.001$ by both the Fisher exact and the Cochran-Armitage tests) elevated incidence of hepatocellular carcinomas or adenomas when compared with nontreated matched controls. From these data, summarized in Appendix B, the U.S. EPA (1980b) calculated a q_1^* for humans of 1.98×10^{-2} (mg/kg/day) $^{-1}$.

6.3.2. Inhalation. No reports of carcinogenicity in humans or animals related to inhalation exposure to 2,4,6-trichlorophenol were located in the available literature; therefore, no q_1^* or carcinogenic potency for inhalation exposure of 2,4,6-trichlorophenol can be calculated.

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APPENDIX A

Summary Table for 2,4,6-Trichlorophenol*

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q ₁ *
Inhalation				ND
Oral	mouse	5000 and 10,000 ppm (650 and 1300 mg/kg/day)	hepatocellular carcinoma and adenoma	1.98×10^{-2} (mg/kg/day) ⁻¹

*Source: NCI, 1979

ND = Not derived

APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound: 2,4,6-trichlorophenol

Reference: NCI, 1979

Species, Strain, Sex: mice, B6C3F1, male

Body weight: 0.04 kg (measured)

Length of exposure (t_e) = 735 days

Length of experiment (L_e) = 735 days

Lifespan of animal (L) = 735 days

Tumor site and type: liver, hepatocellular adenoma and carcinoma

Route, vehicle: oral, diet

Experimental Doses or Exposures (ppm)	Transformed Dose (mg/kg/day)	Incidence
		No. Responding/No. Tested or Examined
0	0	4/20
5000	650	32/49
10,000	1300	39/47

Unadjusted q_1^* from study = $1.61 \times 10^{-3} \text{ (mg/kg/day)}^{-1}$

Human $q_1^* = 1.98 \times 10^{-2} \text{ (mg/kg/day)}^{-1}$